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(54) Treatment of diseases caused by viruses.

(57) A pharmaceutical composition for treating a disease caused by virus comprising

an antiviral agent having no saccharide residue acylated with S-oxoacid and

a glycoside having not less than two monosaccharide residue in which not less than one of the said monosaccharide residues have(has) at least one S-oxoacid group attached to the saccharic carbon atom(s) thereof through a linking group with a low molecular weight, or its pharmaceutically acceptable salt.

EP 0 312 222 A1

TREATMENT OF DISEASES CAUSED BY VIRUSES

BACKGROUND OF THE INVENTION

1. Field of the invention

The present invention relates to treatment, inclusive of prophylaxis and therapy, of diseases caused by viruses. More particularly, the present invention provides pharmaceutical composition (including pharmaceutical composition for veterinary use) containing as an active ingredient a combination of an antiviral agent having no saccharide residue acylated with S-oxoacid with a certain glycoside having at least one S-oxoacid group, which are useful in the treatment of disease caused by viruses; and a method of treating diseases caused by viruses which comprises administering said combination. The combination as described above can produce antiviral synergism and consequently permit enhancement of antiviral effect, while reducing individual dosages and alleviating adverse side-effects.

Very few chemotherapeutic agent for viral diseases have been available which can exert satisfactory therapeutic effects, in contrast to those for bacterial diseases. The compounds, which are effective against viruses in vitro, often produce severe adverse side-effects when administered to living body, and even antiviral agents that are considered as tolerable for practical use find, in many instances, severely restricted application because of their adverse side-effects. This may be reflected, for example, by such antiviral agents as arabinosyladenine (Ara A) or Acyclovir being in recent years found to be effective against herpesviruses and azidothymidine (AZT) being recently reported to possess effects against AIDS (acquired immunodeficiency syndrome) related viruses (that is to say, human Immunodeficiency virus ordinarily referred to briefly as "HIV"); these antiviral agents after being given to man also bring about side-effects such as nausea, emesis, diarrhea, eruption, anemia and phlebitis developed locally at the site of administration, which sometimes leads to forced discontinuation of administration. Under these circumstance, development of antiviral agents with reduced side effects is strongly demanded, while reduction by way of some means of side-effects inherent to the conventional antiviral agents currently constitutes one of the most important research subjects since the latter offers better chance of success.

During the course of an investigation on synergism between various anti-viral agents, the present inventors have attemted a combined use of sulfated glycosides such as glycyrrhizin sulfate which was recently reported as having certain antiviral effect, as well as digitonin sulfate, stevioside sulfate, etc., with the conventional antiviral agents, which has shown a significant synergistic activity of 20 to 50 times greater than that could be expected from simple addition of the individual drug effects. This finding has let us to a valuable pharmaceutical composition based on a new synergistic combination and use thereof in the treatment of virus disease, which are the subject of the present invention.

2. Description of the related art

A comprehensive review on antiviral agents is given in Kirk Othmer's Encyclopedia of Chemical Technology, vol. 5, 542-552. H. Nakashima, et al. (Jpn. J. Cancer Res.(Gann) 78, 767-771, Aug., 1987) descrided the antiviral activity of glycyrrhizin sulfate against HIV.

SUMMARY OF THE INVENTION

In the first aspect, the present invention provides a method of treating a disease caused by virus, which comprises administering to a subject in need of such treatment (a) an antiviral agent having no saccharide residue acylated with S-oxoacid in combination with (b) a glycoside having not less than two monosaccharide residue in which not less than one of the said monosaccharide residues have(has) at least one S-oxoacid group attached to the saccharic carbon atom(s) thereof through a linking group with a low molecular weight, or its pharmaceutically acceptable salt.

In the second aspect, the present invention provide the use of a glycoside having not less than two monosaccharide residue in which not less than one of the said monosaccharide residues have(has) at least one S-oxoacid group attached to the saccharic carbon atom(s) thereof through a linking group with a low

molecular weight, or its pharmaceutically acceptable salt for the manufacture of a medicament effective for treating diseases caused by viruses which medicament is specifically intended to be administered in combination with an antiviral agent having no saccharide residue acylated with S-oxoacid.

In the third aspect, the present invention provides a pharmaceutical composition comprising a synergistically effective amount of each of an antiviral agent having no saccharide residue acylated with S-oxoacid and a glycoside having not less than two monosaccharide residue in which not less than one of the said monosaccharide residues have(has) at least one S-oxoacid group attached to the saccharic carbon atom(s) thereof through a linking group with a low molecular weight, or its pharmaceutically acceptable salt.

In the fourth aspect, the present invention provides the use of a glycoside having not less than two monosaccharide residue in which not less than one of the said monosaccharide residues have(has) at least one S-oxoacid group attached to the saccharic carbon atom(s) thereof through a linking group with a low molecular weight, or its pharmaceutically acceptable salt for the manufacture of an antiviral synergistic composition comprising an antiviral agent having no saccharide residue acylated with S-oxoacid and a glycoside having not less than two monosaccharide residue in which not less than one of the said monosaccharide residues have(has) at least one S-oxoacid group attached to the saccharic carbon atom(s) thereof through a linking group with a low molecular weight, or its pharmaceutically acceptable salt in order to achieve reduction in side effects pertaining to the former antiviral agent.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The term "treatment" as used herein is intended to comprehend all the managements of diseases including prevention, sustention (i.e. prevention of aggravation), alleviation (i.e. amelioration of conditions) and therapy.

The viral diseases to be treated according to the present invention include diseases caused by various viruses. Such viruses include Poxviridae (e.g. smallpoxviruse, rabbitpoxvirus, cowpoxvirus, swinepoxvirus, equinepoxvirus, fowlpoxvirus), Herpesviridae (e.g. herpes symplex virus 1 or 2, herpes zoster virus, cytomegalovirus), Adenoviridae, Orthomyxoviridae (e.g. influenza virus), Paramyxoviridae (e.g. parainfluenza virus, mumps virus, respiratory syncytial virus, measles virus), Rhabdoviridae (e.g. rhavdo virus), Picornaviridae (e.g. poliovirus, coxsackie virus, echovirus, hepatitis virus, rhinovirus), Coronaviridae, Parvoviridae, Reoviridae(or Diplorna virus), Togaviridae (e.g. Japanese encephalitis virus, rubella virus), and Retroviridae (e.g. HIVs (e.g. HTLV-III, LAV, ARV etc.), ovine visna virus, equine infectious anemia virus, avian leukemia virus, avian sarcoma virus, avian reticuloendothetiosis virus, murine breast carcinoma virus, murine leukemia virus, murine sarcoma virus, equine type C virus, hamster type C virus, rat leukemia virus, feline leukemia virus, feline sarcoma virus, feline type C virus, ovine leukemia virus, bovine leukemia virus, swine type C virus, simian leukemia virus, Mason-Pfizer Virus, simian sarcoma virus, simian T-lymphotropic virus, baboon type C virus, adult T-cell leukemia virus (ATLV) or human T-lymphotropic virus types I and II (HTLV-I, HTLV-II), human Kawasaki disease virus), etc. The important diseases are those caused by retrovirus, the most important being AIDS, PGL (Presistent generalized lymphadenopathy), ARC(AIDS-related complex), LAS(Lymphadenopathy syndrome) and human T-cell leukemia.

The antiviral agent having no saccharide residue acylated with S-oxoacid which is useful in this invention, there can be employed any antiviral agents insofar as they lack the said residue, and such antiviral agents include nucleic acid type antiviral agents (for example, 3′-azido-3′-deoxythymidine (azidothymidine or AZT), 2′,3′-dideoxynucleosides (2′,3′-dideoxyadenosine, -guanosine, -inosine, -cytidine, or -thymidine), ribavirin, isoprinosin, acyclovir, Ara A, Ara T, Ara C, iododeoxyuridine (IDU), bromovinyl deoxyuridine, fluoroiodo aracytosin, 2′-amino-2′-deoxyribofuranosyladenine, trifluridine, acyclovir derivatives (deoxy-, glycyl- or iodo-acyclovir, dihydroxypropoxymethyl guanine, dihydroxybutyl guanine), chloroethyldeoxyuridine, toyocamycin, puromycin, etc.), peptide type antiviral agent (e.g., suramin, distamycin A, actinomycin D, etc.), ansamycin type antiviral agent (e.g., ansamycin, rifamycin, rifampicin, dimethylbenzyl rifampicin, streptovaricin S, etc.), polyanionic type antiviral agents (e.g., HPA-23 ($NaSb_9W_{21}O_{86}$), etc.), thiosemicarbatide type antiviral agents (imuthiol, isatin-beta-thiosemicarbazone (IBT), marboran, etc.), phosphoric acid type antiviral agent (e.g., foscarnet), amantadine type antiviral agent (e.g., amantadine, rimantadine, N′-methyladamantane-spiro-3′-pyrolidine hydrochloride, etc.), endogenous antiviral agent (e.g., interferons, interleukins, Neurotropin), glycoside type antiviral agent (e.g., glycyrrhizin, etc.) and lipid type antiviral agent (e.g. AL721 etc.). The term "saccharide esterified with S-oxoacid" has the meaning as the saccharide residue having S-oxoacid group in "glycoside acylated with S-oxoacid" as described below.

Preferred antiviral agents are those having reverse transcriptase inhibitory activity and effective against HIV (AZT, 2′,3′-dideoxynucleosides, suramin, ansamycin, HPA-23, foscarnet), and other agents not having

reverse transcriptase inhibitory activity but effective against HIVs (ribavirin, α-, β-interferons, AL721, ampligen).

The term "glycoside having not less than two monosaccharide residues where not less than one of the said monosaccharide residues has(have) at least one S-oxoacid group attached to the saccharic carbon atom(s) thereof through a linking group with a low molecular weight"(this is referred to hereinafter as "glycoside acylated with S-oxoacid") to be used in the present invention includes natural or synthetic glycosides which have not less than two (e.g. 2, 3, 4, 5 or more) saccharide residues having S-oxoacid group attached to the saccharic carbon atom thereof through a linking group with a low molecular weight.

The term "glycoside" refers to saccharide derivatives in which a non-saccharide group (aglycone) is attached by the atom, such as oxygen, nitrogen, sulfate, etc.

The term "matural glycoside" means the glycosides which can be obtained by way of such means as extraction from natural resources, such as plants, microbes or animals.

The term "synthetic glycoside" refers to the glycosides which can be obtained by binding one or more saccharic group onto an aglycone, a glycoside having one monosaccharic residue or a glycoside having not less than two monosacharic residues by chemical synthesis or biochemical synthesis (e.g. by enzime).

Such natural or synthetic glycosides include a phenol glycoside, a nitrile glycoside, a coumarin glycoside, an anthracene glycoside, a terpene glycoside, a bitterness glycoside, a flavone glycoside, an isoflavone glycoside, a flavonol glycoside, a flavanoe glycoside, a pelargonidin glycoside, a cyanidin glycoside, a delphinidin glycoside, a steroid glycoside, a triterpenoid glycoside, a cardiotonic glycoside, an indoxyl glycoside, a gibberellin glycoside, an S-glycoside, a C-glycoside, a C,O-mixed glycoside, etc., and important among them are a triterpenoid glycoside, a steroid glycoside and a terpene glycoside.

Examples of glycosides include lotusin , sennoside A or B, stevioside, apiin, kaempferitrin, kaempferin, butrin, salvianin, pelargonin, monardein, cyanin, peonin, mecocyanin, lycoricyanin, delphinin, delphin, nasunin, hyacin, violanin, malvin, amolonin, osladin, kammonin, sarsasaponin, dioscin, digitonin, gitonin, convallasaponin C or D, glucoconvallasaponin A or B, tigonin, asiaticoside, aescin, glycyrrhizin, cyclamin, theasaponins, camellia saponins, α-hederin, spirasaponin A or B, solasonine, solanine, tomatine, lucenin-1, xylosylglucosyl apigenin and saponarin.

The glycoside acylated with S-oxoacid may have at least one but normally not more than four S-oxoacid groups on at least one, a minor portion, a major portion or all of the constituent monosaccharides.

The S-oxoacid group includes sulfo group ($-SO_3H$) and hydroxysulfinyl group (-SO.OH), with sulfo group being preferred.

The term "acylated" includes "esterified", "amidated" and "C-acylated".

The term "saccharic carbon atom" refers to a carbon atom which costitute a chain skeleton, a tetrahydrofuran ring or tetrahydropyran ring contained in saccharides..

The term "low-molecular-weight linking group" is intended to comprehend oxy (-O-), imino (-NH-), thio (-S-), methylene ($-CH_2-$), ethylidene ($-CH(CH_3)-$) groups and the like. The term "lower molecular weight" means molecular weights of any linking groups ranging from about 14 to about 32. The preferred linking group includes oxy and imino.

The saccharides (serving as a repeating unit) includes, xylose, arabinose, rhamnose, fucose, glucose, galactose, glucuronic acid, galacturonic acid, mannuronic acid, etc.

Among such glycosides acylated with S-oxoacid are included known ones and novel ones. Such novel glycosides acylated with S-oxoacid can be produced by the same procedure as empolyed for known ones, with an example of such production procedures being described in the following.

Chlorosulfonic acid is added dropwise to dry pyridine in volume 8 to 10 times that of chlorosulfonic acid, while cooling, and a small amount each of formamide and a glycoside (in amounts about one-fourth of chlorosulfonic acid) are added to the mixture, followed by heating at 55 -65 $^{\circ}$ C under stirring. After stirring the mixture for several hours, the solvent is distilled off, and the residue is purified for example by reprecipitation, recrystallization, etc.

The term "pharmaceutically acceptable salts" is intended to designate salts which retain biological activity of the parent compounds but not exhibit any adverse toxicity at normal dose levels. Such salts include the salts of inorganic bases, such as sodium, potassium, and ammonium salts, salts with organic bases, such as diethanolamine and amino acid salts. These salts can be produced from their corresponding free acids.

The above antiviral agent and the glycoside acylated with S-oxoacid may be administered concurrently or sequentially. However, both of them should in principle be administered on the same day, optionally at different points of time in the same day but as close to each other as possible. Naturally, these two kinds of active ingredients may be administered simultaneously in the form of a combination of their individual pharmaceutical preparations or they may be contained in the same, single pharmaceutical preparation.

Such combination is optionally selected depending upon the conditions of patients, kind of diseases, etc.

The dosage of the antiviral agent may be such an amount as may be sufficient to realize the concentration permitting development of antiviral activity in body, even when it is administered alone. Since the present invention can produce synergism, nevertheless, the antiviral agent may in some instances be given in doses less than the amount to producing the above described concentration, for example, 1/2 to 1/200, 1/10 to 1/100 or 1/20 to 1/50 of the said amount. The specific dosage can vary largely depending upon the type and nature of the individual pharmaceutical preparations, and may be changed with the conditions of patients, kind of diseases, and type and amount of the glycoside acylated with S-oxoacid to be combined, etc. For example, Amantadin may be administered at a daily dose of 15 - 150 mg, with Methisazone being given at a daily dose of 20 - 400 mg/kg.

The glycoside acylated with S-oxoacid, whether or not they have antiviral activity. The dosage of the agent having antiviral activity may be such an amount as may be sufficient to realize the concentration permitting development of antiviral activity in body, even when it is administered solely. Since the present invention can produce antiviral synergism, however, the agent may be in some instances be given in doses less than the amount producing the above-described concentration, for example, 1/2 to 1/500, 1/5 to 1/200, or 1/20 to 1/50 of the said amount. The specific dosage of the agent may in any case vary depending on the nature of individual agents, condition of patients, kind of diseases and type and amount of the antiviral agent to be combined, and generally ranges from 0.02 to 200 mg/kg, preferably 0.1 - 100 mg/kg, with the agent being administered to human being at a daily dose of about 1 mg to 10 g/day, preferably about 5 mg to 5 g/day.

Each of the above pharmaceutical preparations may be administered once a day or as divided into two to six times or as a sustained release dosage form.

The administration can be made through any optional routes, such as by oral and topical application and injection.

For administration, the active ingredients may be mixed with a pharmaceutical carrier, such as organic or inorganic solid or liquid excipient, being suitable for such administration route as oral administration, injection, etc. processed in the form of the conventional pharmaceutical preparations. Such pharmaceutical preparations include solid ones, such as tablets, granules, powders and capsules, and liquid ones such as solutions, emulsions and suspensions. The above carriers include, for example, starch, lactose, glucose, sucrose, dextrins, celluloses, paraffins, fatty acid glycerides, water, alcohols, gum arabic. If necessary, there may be added adjuvants, stabilizers, emulsifiers, lubricants, binders, pH-regulating agents, isotonic agents, and other conventional additives.

This invention also provides a synergist for promotting antiviral activity of an antiviral agent having no saccharide residue acylated with S-oxoacid, which comprises a glycoside having not less than two monosaccharide residues have(has) at least one S-oxoacid group attached to the saccharide carbon atom thereof through a linking group with a low molecular weight, and a method for treating diseases caused by virus, which comprises administering an effective amount of the pharmaceutical composition of this invention to a subject (animal or human) in need of such treatment.

The following examples will illustrate the present invention in further detail.

The examples are given below to illustrate this invention in more detail, with the test examples being also described to clarify the effects of this invention.

Preparation 1

Preparation of sulfated glycyrrhizin

Glycyrrhizin (5g) was added to 95 % sulfuric acid (10 ml) cooled to below -25 °C with stirring. After the reaction mixture was stirred at the same temperature for 90 minutes, the reaction solution was gradually poured onto ice (120 g) with stirring. To the resulting solution was gradually added calcium carbonate with well stirring. The precipitates were filtered off with suction, and, then washed. To the combined filtrates added ethanol to the final concentration of 20%(v/v), and the resulting solution was kept to stand overnight at 5 °C to precipitate calcium sulfate. The precipitates were filtered off, and the filtrate was adjusted to pH 10 with sodium carbonate. After addition of acetic acid to make the solution weakly acidic, the solution was concentrated to about 20 ml, then diluted with ethanol (100 ml), and kept to stand overnight at 5 °C. The precipitates formed in the solution were isolated with centrifugation, washed with ethanol, and with ether, and dried under vaccum to give the white powders of the title compound.

Example 1

(A)	Sodium glycyrrhizin sulfate	300 mg
	Corn starch	45 "
	Lactose	300 "
	Magnesium stearate	5 "

The above ingredients are mixed, granulated and pressed into tablets and according to the conventional procedure.

(B)	3′-Azido-3′-deoxythymidine	25 mg
	Corn starch	120 "
	Lactose	300 "
	Magnesium stearate	5 "

The above ingredients are mixed and filled in hard gelatine capsules and according to the conventional procedure.

(A) and (B) are combined into a dose form.

Example 2

Sodium glycyrrhizin sulfate	120 mg
3′-Azido-3′-deoxythymidine	100 "
0.9 % saline	q.s. to 10 ml

The above ingredients are mixed and dissolved according to the conventional procedure to form an injectable solution.

Example 3

Sodium stevioside sulfate	200 units
3′-Azido-3′-deoxythymidine	50 mg
0.9 % Saline	q.s. to 10 ml

Example 4

Sodium digitonin sulfate	500 units
Ara C	10 mg
Procain hydrochloride	10 mg
Water	q.s. to 10 ml

Example 5 (Inhibition of viral infection)

AIDS virus HTLV-III/LAV was challenged to established human T-lymphocyte culture cells MT-4 and the

cell suspension and virus particles were incubated at 37°C for 1 hour. The cells were then washed with phosphate buffered saline once and cultured with or without various doses of the test substances in RPMI-1640 medium at 37°C under 5 % CO_2 in an incubator.

MT-4 cells infected with HTLV-III were destructed as the virus proliferated, resulting in decrease of viable cells. Prior to the cytolysis by viral cytopathic effect, the cells infected with HTLV-III appeared which were detectable by indirct immuno fluorescence method. On day 12, number of the living cells was counted to know the extent of infection, and rate of the infected cells was determined by indirect immuno-fluorescence method using an antibody having specificity to the virus specific antigen. As the test substances, 3′-azido-3′-deoxythymidine (AZT) and glycyrrhizin sulfate, digitonin sulfate, stevioside sulfate were used. The results are shown in the following table.

AZT	0nM	10nM	50nM
glycyrrhizin sulfate(μg/ml)			
0	100	100	100
100	100	80	80
250	100	60	25
AZT	0nM	10nM	50nM
digitonin sulfate(μg/ml)			
0	100	100	100
100	100	60	60
250	80	60	10
AZT	0nM	10nM	50nM
stevioside sulfate(μg/ml)			
0	100	100	100
100	100	80	40
250	80	50	10

It is evident from these results that the conbined use of the above two substances can produce significant synergistic effect.

Claims

1. A pharmaceutical composition for treating a disease caused by virus comprising
(a) an antiviral agent having no saccharide residue acylated with S-oxoacid and
(b) a glycoside having not less than two monosaccharide residue in which not less than one of the said monosaccharide residues have(has) at least one S-oxoacid group attached to the saccharic carbon atom(s) thereof through a linking group with a low molecular weight, or its pharmaceutically acceptable salt.

2. The composition according to claim 1, wherein the said antiviral agent is present in an amount lower than its antivirally effective dose by itself.

3. The composition according to claim 1, wherein the said antiviral agent is a nucleic acid type antiviral agent.

4. The composition according to claim 3, wherein the said nucleic acid type antiviral agent is selected from the group consisting of 3′-azido-3′-deoxythymidine(AZT), 2′,3′-dideoxythymidine, 2′,3′-dideoxyadenosine, 2′,3′-dideoxyguanosine, 2′,3′-dideoxyinosine, 2′,3′-dideoxycytidine, Ara A, Ara C, Ara T, iododeoxyuridine and Acyclovir.

5. The composition according to claim 1, wherein not less than two saccharide residues in the glycoside are present in succession.

6. The composition according to claim 1, wherein the glycoside is selected from (i) triterpenoid glycoside, (ii) steroid glycoside and (iii) terpene glycoside.

7. The composition according to claim 6, wherein the said glycoside is selected from (i) glycyrrhizin, (ii) digitonin and (iii) stevioside.

8. The composition according to claim 1, wherein the said S-oxoacid group is a sulfo group ($-SO_3H$).

9. The composition according to claim 1, wherein the linking group is an oxy group (-O-).

10. The composition according to claim 1, wherein the disease caused by virus is that caused by retrovirus.

11. The composition according to claim 10, wherein the retrovirus is human retrovirus.

12. The composition according to claim 11, wherein the human retrovirus is selected from HTLV-I, HTLV-II, HTLV-III, LAV, ARV and Kawasaki disease virus.

13. The composition according to claim 1, wherein the viral disease is Lymphadenopathy syndrome-(LAS), Persistent generalized lymphadenopathy(PGL), AIDS, AIDS-related complex(ARC), Adult T-cell leukemia(ATL) or Kawasaki disease.

14. A synergist for promoting antiviral activity of an antiviral agent having no saccharide residue acylated with S-oxoacid, comprising a glycoside having not less than two monosaccharide residues wherein not less than one of the said monosaccharide residues have at least one S-oxoacid group attached to the saccharic carbon atom(s) thereof through a linking group with a low molecular weight or its pharmaceutically acceptable salt.

15. A use of treating a disease caused by virus comprising

(a) an antiviral agent having no saccharide residue acylated with S-oxoacid and

(b) a gylcoside having not less than two monosaccharide residue in which not less than one of the said monosaccharide residues have(has) at least one S-oxoacid group attached to the saccharic carbon atom(s) thereof through a linking group with a low molecular weight, or its pharmaceutically acceptable salt.

16. The use according to claim 15, wherein the said antiviral agent is present in an amount lower than its antivirally effective dose by itself.

17. The use according to claim 15, wherein the said antiviral agent is a nucleic acid type antiviral agent.

18. The use according to claim 17, wherein the said nucleic acid type antiviral agent is selected from the group consisting of 3′-azido-3′-deoxythymidine(AZT), 2′,3′-dideoxythymidine, 2′,3′-dideoxyadenosine, 2′,3′-dideoxyguanosine, 2′,3′-dideoxyinosine, 2′,3′-dideoxycytidine, Ara A, Ara C, Ara T, iododeoxyuridine and Acyclovir.

19. The use according to claim 15, wherein not less than two saccharide residues in the glycoside are present in succession.

20. The use according to claim 15, wherein the glycoside is selected from (i) triterpenoid glycoside, (ii) steroid glycoside and (iii) terpene glycoside.

21. The use according to claim 20, wherein the said glycoside is selected from (i) glycyrrhizin, (ii) digitonin and (iii) stevioside.

22. The use according to claim 15, wherein the said S-oxoacid group is a sulfo group ($-SO_3H$).

23. The use according to claim 15, wherein the linking group is an oxy group (-O-).

24. The use according to claim 15, wherein the disease caused by virus is that caused by retrovirus.

25. The use according to claim 24, wherein the retrovirus is human retrovirus.

26. The use according to claim 25, wherein the human retrovirus is selected from HTLV-I, HTLV-II, HTLV-III, LAV, ARV and Kawasaki disease virus.

27. The use according to claim 15, wherein the viral disease is Lymphadenopathy syndrome(LAS), Persistent generalized lymphadenopathy(PGL), AIDS, AIDS-related complex(ARC), Adult T-cell leukemia-(ATL) or Kawasaki disease.

28. The use according to claim 15, wherein the antiviral agent having no saccharide residue acylated with S-oxoacid and the gylcoside having not less than two monosaccharide residue wherein not less than one of the said monosaccharide residues have at least one S-oxoacid group attached to the saccharic carbon atom(s) thereof through a linking group with a low molecular weight, or its pharmaceutically acceptable salt are administered simultaneously and/or sequentially.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 88 30 8972

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
Y	US-A-4 678 772 (R. SEGAL) * Column 6, lines 50-58; claims 1-2 * ---	1-28	A 61 K 31/725 A 61 K 31/70 // (A 61 K 31/725 A 61 K 31:70)
D,Y	CHEMICAL ABSTRACTS, vol. 107, no. 23, 7th December 1987, page 24, no. 211581f, Columbus, Ohio, US; H. NAKASHIMA et al.: "A new anti-human immuno-deficiency virus substance, glycyrrhizin sulfate: endowment of glycyrrhizin with reverse transcriptase-inhibitory activity by chemical modification", & JPN. J. CANCER RES. (GANN) 1987, 78(8), 767-71 * Abstract * -----	1-28	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	24-01-1989	BRINKMANN C.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P0401)